Progression-free and overall survival for concurrent nivolumab with standard concurrent chemo-radiotherapy in locally advanced stage IIIA/B NSCLC: Results from the European Thoracic Oncology Platform NICOLAS phase II trial (ETOP 6-14)

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Abstract: Background: NICOLAS is the first completed single-arm phase II trial in stage III NSCLC examining hierarchically first the safety and then the efficacy of adding nivolumab concurrently to standard definitive concurrent chemo-radiotherapy. The safety endpoint was reported earlier; here we present the efficacy results. Methods: Stage IIIA/B unresectable treatment-naive NSCLC patients received 3 cycles of platinum-based chemotherapy and concurrent radiotherapy (66Gy/33fractions), along with nivolumab (360mg/Q3W). Nivolumab was continued as monotherapy consolidation for a maximum of one year (480mg/Q4W). The primary endpoint was 1-year PFS, with a target improvement compared to historical data of at least 15%, from 45% to 60%. For testing this efficacy hypothesis, a sample size of 74 evaluable patients provides power 83%, at 1-sided alpha 5%. Findings: 79 patients were enrolled with median follow-up 21.0 months (m) (Interquartile Range:15.8m-25.8m) for the primary PFS analysis. 35.4% of patients had stage IIIA and 63.3% stage IIIB. The 1-year PFS was 53.7% (95%CI[42.0%-64.0%]), the median PFS 12.7m (95%CI[10.1m-22.8m]). Since among the 74 first evaluable patients, 37 PFS events occurred in the first year post-treatment, a 1-year PFS rate of 45% could not be rejected (p-value=0.23). At an extended follow-up (32.6m median), 37 deaths have been recorded, with a median OS 38.8m(95%CI[26.8m-Not Estimable]) and a 2-year OS rate of 63.7% (95%CI[51.9%-73.4%]). The OS of stage IIIA patients was found to be significantly higher than stage IIIB patients, with 2-year OS 81% and 56% respectively (p=0.037). Conclusion: PFS and OS are arithmetically higher to studies in the same population, however, based on the formal hierarchical efficacy analysis, we could not reject that the 1-year PFS rate is 45%.

DOI: https://doi.org/10.1016/j.jtho.2020.10.129

Progression-free and overall survival for concurrent nivolumab with standard concurrent chemo-radiotherapy in locally advanced stage IIIA/B NSCLC: Results from the European Thoracic Oncology Platform NICOLAS phase II trial (ETOP 6-14). Journal of Thoracic Oncology, 16(2):278-288.
DOI: https://doi.org/10.1016/j.jtho.2020.10.129

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PII: S1556-0864(20)30995-3

DOI: https://doi.org/10.1016/j.jtho.2020.10.129

Reference: JTHO 1972

To appear in: *Journal of Thoracic Oncology*

Received Date: 25 June 2020

Revised Date: 19 October 2020

Accepted Date: 21 October 2020

Please cite this article as: Peters S, Felip E, Dafni U, Tufman A, Guckenberger M, Álvarez R, Nadal E, Becker A, Vees H, Pless M, Martinez-Marti A, Lambrecht M, Andratschke N, Tsourti Z, Piguet A-C, Roschitzki-Voser H, Gasca-Ruchti A, Vansteenkiste J, Stahel RA, Ruysscher DD, Progression-free and overall survival for concurrent nivolumab with standard concurrent chemo-radiotherapy in locally advanced stage IIIA/B NSCLC: Results from the European Thoracic Oncology Platform NICOLAS phase II trial (ETOP 6-14)., *Journal of Thoracic Oncology* (2020), doi: https://doi.org/10.1016/j.jtho.2020.10.129.

NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

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NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

Summary

Background: NICOLAS is the first completed single-arm phase II trial in stage III NSCLC examining hierarchically first the safety and then the efficacy of adding nivolumab concurrently to standard definitive concurrent chemo-radiotherapy. The safety endpoint was reported earlier; here we present the efficacy results.

Methods: Stage IIIA/B unresectable treatment-naive NSCLC patients received 3 cycles of platinum-based chemotherapy and concurrent radiotherapy (66Gy/33fractions), along with nivolumab (360mg/Q3W). Nivolumab was continued as monotherapy consolidation for a maximum of one year (480mg/Q4W). The primary endpoint was 1-year PFS, with a target improvement compared to historical data of at least 15%, from 45% to 60%. For testing this efficacy hypothesis, a sample size of 74 evaluable patients provides power 83%, at 1-sided alpha 5%.

Findings: 79 patients were enrolled with median follow-up 21.0 months (m) (Interquartile Range:15.8m-25.8m) for the primary PFS analysis. 35.4% of patients had stage IIIA and 63.3% stage IIIB. The 1-year PFS was 53.7% (95%CI[42.0%-64.0%]), the median PFS 12.7m (95%CI[10.1m-22.8m]). Since among the 74 first evaluable patients, 37 PFS events occurred in the first year post-treatment, a 1-year PFS rate of ≤45% could not be rejected (p-value=0.23). At an extended follow-up (32.6m median), 37 deaths have been recorded, with a median OS 38.8m(95%CI[26.8m-Not Estimable]) and a 2-year OS rate of 63.7% (95%CI[51.9%-73.4%]). The OS of stage IIIA patients was found to be significantly higher than stage IIIB patients, with 2-year OS 81% and 56% respectively (p=0.037).

Conclusion: PFS and OS are arithmetically higher to studies in the same population, however, based on the formal hierarchical efficacy analysis, we could not reject that the 1-year PFS rate is ≤45%.

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INTRODUCTION

Stage III non-small cell lung cancer (NSCLC) represent approximately 25% of all NSCLC patients at diagnosis.[1] The treatment of choice for fit patients with unresectable or multi-level N2 or any N3 disease is concurrent chemo-radiotherapy (CCRT).[1] The combination of a platinum-based doublet chemotherapy given together with 60-66 Gy in 2 Gy fractions of radiotherapy is considered standard of care.[1] Although in highly selected patients, the five-year overall survival (OS) may reach up to 33%,[2,3] most series report a more sobering 25% OS rate.[4,5] These inter-trial differences may be due to patient selection, as stage III NSCLCs represents an extremely heterogeneous group of diseases.

The addition of 1 year of durvalumab after completion of CCRT has recently shown to improve 3-year OS by more than 10%.[6] However, as most patients still suffer from disease recurrence, with a subsequent 57% survival rate at 3 years in that study, further improvements are still necessary.

The concurrent administration of an anti-PD(L)-1 with radiotherapy may improve the response rate in preclinical models,[7] with some synergy suggested in retrospective datasets.[8,9] Similarly, in metastatic patients, concurrent platinum-based chemotherapy and anti-PD-(L)1 is the treatment of choice in all frontline stage IV patients irrespective of any biomarker, including patients with NSCLC characterized by a low PD-L1 expression.[10]

The concurrent administration of immune checkpoint inhibitors with CCRT, followed by 12 months of consolidation is a rational approach that ultimately may improve the OS over CCRT followed by durvalumab. The NICOLAS single-arm phase II trial combined nivolumab delivered for the first time concurrently with standard CCRT, using definitive radiation with standard fractionation doses, followed by a maximum of 12 months of nivolumab consolidation therapy.

We hierarchically tested the safety and efficacy of this regimen. The safety analysis has been reported earlier.

Here, we report the results of the hierarchically tested primary endpoint of 1-year progression-free survival (PFS). Updated results for safety as well as information on OS and secondary efficacy endpoints are also provided.

METHODS

Patient population

The trial included patients from 10 European centres in five countries (Belgium, Germany, Spain, Switzerland and The Netherlands).

Patient eligibility criteria included, as previously reported,[11] age ≥18 years, pathologically confirmed locally advanced stage IIIA/B NSCLC (7th TNM classification), nodal status N2 or N3, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, life expectancy greater than three months, as well as adequate haematological, liver and renal function. Patients with prior chemo-, radio- or molecular targeted therapy, or mixed small and non-small-cell histologic features were excluded.

Trial design and treatment administration

The history of the trial, and corresponding amendments have been previously described in detail.[11] Protocol version 3.0 (v3) called for an efficacy evaluation focusing on only the patients receiving nivolumab concurrently with CCRT (supplement, Figure 1). Beyond the safety evaluation, the additional aim was to explore through a hierarchical design, the efficacy of the combination treatment. A corresponding increase of sample size was planned to enable the efficacy analysis in 74 evaluable patients. The primary efficacy endpoint, 1-year PFS rate, was designed to be tested, only conditional on proven adequate safety of the concurrent addition of nivolumab to chemo-radiotherapy.

Three cycles of chemotherapy with cisplatin or carboplatin combined with either vinorelbine, etoposide or pemetrexed (non-squamous histology) were required. Delivery of the first induction cycle of platinum-based chemotherapy before inclusion in the trial was part of the protocol, in order to homogenize treatment and take into account potential radiotherapy planning delays in some participating centres. Radiotherapy, 66 Gy in 33 once-daily fractions to the primary tumour and the involved lymph nodes,[12] was delivered concurrently with the second and third chemotherapy cycle. Patients received four doses of nivolumab of 360 mg at a three-week cycle, the first two concurrently with standard platinum-based chemotherapy and radiotherapy, starting from the first day of chemo-radiotherapy, followed by 480 mg at a four-week cycle for up to one year from start of nivolumab treatment.

Ethics committees and relevant health authorities approved the trial protocol. This trial was registered with ClinicalTrials.gov, number NCT02434081.

Endpoints

The primary endpoint, to be hierarchically tested after safety was proven, was PFS rate at 1-year. Start date for time-to-event endpoints was the date of 1st chemotherapy cycle. PFS was defined as the time from start date until a documented progression of disease according to RECIST v1.1 or death, if no documented progression had occurred. Tumour assessments by CT scans were performed every 9 weeks for the first year from enrolment, every 12 weeks for the second year and every six months afterwards.

Secondary endpoints were OS (time from start date to death from any cause), objective response (OR) rate of patients, according to RECIST v1.1 criteria (best overall response, complete (CR) or partial response (PR), across all assessment time-points from enrolment to termination of protocol treatment), duration of response (DoR) (time from first OR documentation until documented progression), time-to-treatment failure (TTF) (time from enrolment until any kind of treatment failure, including discontinuation due to toxicity, progression, death, withdrawal or lost-to-follow-up) and time to first pneumonitis incidence of grade ≥3 (time from enrolment until first such documented pneumonitis).

Statistical analysis

According to the hierarchical design of the trial, the efficacy hypothesis would be tested only if the safety null hypothesis was rejected, either at the interim or the final safety analysis. This condition was satisfied, since the safety null hypothesis has been rejected at the interim analysis, as previously published.[11]

The aim of the efficacy testing was to detect an increase in the 1-year PFS rate from ≤45% (P_0) to at least 60% (P_1) under concurrent nivolumab administration with CCRT. Using a 5% one-sided type I error and 83% power, a sample size of 74 patients was needed for testing this efficacy hypothesis according to the exact binomial test for single proportion. At least 41 out of the 74 patients had to reach one year without a PFS event in order to reject the null hypothesis. No formal efficacy interim analysis was planned for the trial.

The event date for PFS was the first of either the imaging date of the first tumour assessment (TA) showing progression of disease (PD) or the date of death. Censoring date for PFS was the last TA date without event, while for OS, the date of last available contact with the patient while still alive. The estimation of all time-to-event endpoints was based on the product-limit Kaplan-Meier method.

NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

Further analysis of PFS, OS and other secondary efficacy endpoints was performed on all patients enrolled in the CCRT cohort, while adverse events (AE) classified according to the CTCAE v4.0, are presented for the safety cohort. More details on statistical analysis are provided in the supplement.

All statistical results were produced using SAS version 9.4.

Interim safety analyses were performed in three-month intervals and reviewed by the European Thoracic Oncology Platform (ETOP) independent data monitoring committee (IDMC).

RESULTS

Analysis Cohorts

The primary efficacy analysis was performed on the cohort consisting of the first 74 evaluable patients on CCRT, up to the primary efficacy analysis cut-off of August 2019. These patients had either reached 1-year tumour assessment without a PFS event or had earlier experienced a PFS event. For completeness purposes, all other results except for the primary analysis are presented for all 79 patients on the CCRT regimen (full CCRT cohort, Figure 1). This cohort includes all patients enrolled on CCRT, irrespective of whether they received any dose of study treatment (intention-to-treat population). The safety cohort consists of the 77 patients who received at least one dose of treatment after enrolment.

Patient and treatment characteristics

A total of 79 patients were enrolled in the study from 14/09/2016 to 6/08/2018. The patient and treatment characteristics for the full CCRT cohort are presented in Table 1. The median follow-up of 21 months (Interquartile Range (IQR): 15.8m-25.8m) captures all follow-up up to completion of one year on study of the last enrolled patient, (database cut-off: 21 August 2019; queried/final: 18 September 2019).

Of the 79 NICOLAS patients in the full cohort, 77 started protocol treatment (two died before treatment start). The median age of patients was 62 years [IQR: 41-78], the majority were male (67.1%), had non-squamous histology (59.5%) and stage IIIB (63.3%), were former smokers (68.4%), and with ECOG PS at enrolment of 1 (51.9%). Chemotherapy constituted cisplatin-based combination with etoposide, pemetrexed or vinorelbine in 65 (84.0%) patients while a carboplatin-based combination was used for 12 patients (15%). After completion of the CCRT and nivolumab part, the majority of the patients (54.5%) had PS 1.

NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

All three chemotherapy cycles were completed for 73 and radiotherapy (at least 60 Gy) for 72 patients. Per protocol, treatment of nivolumab was completed successfully in 31 patients (39.2%). The overall median number of nivolumab doses was 11 (IQR: 1-15). From the total of 46 treatment discontinuations, five occurred during the CCRT-nivolumab phase (two toxicities: stroke and febrile neutropenia; two disease progressions and one investigator's decision). For the 41 treatment discontinuations during the nivolumab-alone phase, recorded reasons were 18 toxicities, 18 progressions, two deaths, one withdrawal, one investigator's decision, and one unspecified (a patient for longer than six weeks without treatment). Forty-nine (62%) patients were still on follow-up at final analysis time.

Primary efficacy analysis: 1-year PFS

As previously mentioned, the 1-year PFS analysis was based on the primary efficacy analysis cohort, which according to the design includes the first 74 evaluable patients who either completed 1-year of follow-up without an event or had a PFS event up to the 1-year time-point. This cohort does not take into consideration two patients who died before treatment start, one who withdrew 2.6 months after enrolment as well as the last two enrolled patients who reached 1-year follow-up later. To reject the null efficacy hypothesis, at least 41 patients from a total of 74 patients on CCRT treatment, should have reached 1-year progression free. The required number was not reached. Only 37 patients were free of progression at one year. Thus, the null hypothesis of 1-year PFS rate ≤45% could not be rejected (exact binomial test p-value=0.23). If the analysis takes into account the two patients who died before treatment and/or the withdrawn patient, the conclusion remains the same.

For the primary efficacy cohort of 74 patients, the estimated from the Kaplan-Meier curve PFS at 1-year is 50.0% (95%CI [39.9%-60.1%]) (Figure S1).

Secondary analyses (full CCRT cohort)

Progression-free Survival

Among all the 79 patients enrolled in the CCRT regimen, 49 (62.0%) PFS events were observed, with 40 occurring by 1 year. Progression was documented for 36 patients, with 15 of them subsequently dying, while 13 patients died without documented progression (with reason of death: lung cancer (3), stroke (2), toxicity/pneumonitis, sepsis/infection, myocarditis, other (5)). PFS at one year is estimated to be 53.7% (95%CI

[42.0%-64.0%]) and median PFS is 12.7 months (95%CI [10.1m-22.8m])(Figure 2a). For the 28 patients with squamous histology, 20 (71.4%) PFS events were recorded with 1-year PFS of 53.6% (95%CI [33.8%-69.8%]) and a median PFS of 12.7 months (95%CI [10.1m-22.8m]), while among the 47 non-squamous histology patients, 26 (55.3%) events occurred, with 1-year PFS of 54.4% (95%CI [39.1%-67.4%]) and median 12.4 months (95%CI [7.2m-NE]) (Figure S2A). Fourteen (50.0%) PFS events were recorded among the 28 stage IIIA patients (1-year PFS: 62.6%, 95%CI [41.6%-77.9%]; median PFS of 27.4 months, 95%CI [7.2m-NE]) and 34 (68.0%) events out of the 50 stage IIIB patients (1-year PFS: 50.0%, 95%CI [35.6%-62.8%]; median 12.1 months, 95%CI [8.9m-17.8m]) (Figure S2B). Statistically significant differences were not observed, neither between the histology nor between the stage subgroups (p-value=0.59 and 0.11, respectively).

None of the variables examined in univariate or multivariate Cox models yielded any statistically significant effect on PFS (all p-values>>0.05) (Figures 2b, S2).

Overall survival

OS results are presented here as of September 2020, analysed beyond the cut-off for the primary PFS analysis, with a median follow-up of 32.6 months (IQR: 26.3m-39.4m). Among the 79 patients, 37 (46.8%) deaths were observed, with a median OS of 38.8 months (95%CI [26.8m-NE]), 1-year OS rate 75.7% (95%CI[64.6%-83.7%] and 2-year OS rate 63.7% (95%CI[51.9%-73.4%]). Most deaths (20; 54.1%) were attributed to lung cancer and one to toxicity (pneumonitis along with tumour progression), while other reported reasons included stroke (n=2), sepsis, cardiac, oesophageal ulcer with haemorrhage, myelodysplastic syndrome, pericarditis carcinomatosa, pneumonia, pulmonary embolism (uncertain whether it was death due to pulmonary fibrosis or myocarditis), necrotizing colitis and severe anaemia (one each). Death reason was not reported for five cases. Relation to treatment was assessed for the deaths recorded as adverse events (8 fatal adverse events at least possibly related to one of the treatments administered).

In univariate analyses, no statistically significant difference in OS was found between the histological subgroups (p-value=0.35; Figure 3A) or other variables, except for stage when comparing stage IIIA to IIIB (log-rank p-value=0.037; Figure 3B). Eight (28.6%) deaths occurred among the 28 stage IIIA patients with 2-year OS of 81.0% (95%CI [60.1%-91.7%]) and 28 (56.0%) deaths among the 50 stage IIIB patients with 2-year OS of 55.6% (95%CI [40.8%-68.2%]). The median OS was 28.6 months for the IIIB patient subgroup (95%CI [12.8m-41.4m]), while not reached for the IIIA subgroup (95%CI [27.4m-NE]).

NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

In the multivariate Cox model, stage remains significant (Cox Wald p-value=0.029), along with age (p-value=0.046) (Figures 3, S3).

Objective response rate

The ORR was 73.4% (95%CI [62.3%-82.7%]), with five (6.3%) CRs. For five patients only the baseline tumour assessment was available before treatment discontinuation. For the 58 patients with documented OR, the median DoR was 11.0 months (95%CI [8.6m-20.7m]) with 33 (56.9%) of them progressing afterwards (Figure S4). Sixty out of 79 patients (76.0%) achieved at least a partial remission of their target lesions. with 58 of them achieving objective response (53 PR, 5 CR; RECIST v1.1), during treatment. Change from baseline for targeted lesion size is presented in Figure 4.

Time to treatment failure

In total, 58 (73.4%) treatment failures were observed with 1-year TTF of 41.8% (95%CI [30.8%-52.3%]) and median 9.2 months (95%CI [6.4m-12.4m]). For 10 (32.3%) of the 31 patients who completed the 1-year nivolumab per-protocol, failure was due to progression (7 patients), death (2 patients) or withdrawal (1 patient).

Time to first pneumonitis of grade≥3 (TFP3)

Nine (11.7%) pneumonitis events of grade≥3 occurred among the 79 patients. All occurred within 1-year of follow-up, with corresponding 1-year TFP3 of 87.0% (95%CI [76.4%-93.0%]; median: NE) (Table S1).

Site of progression and tumour change

In the majority of the 36 documented progressions (27; 75.0%) distant metastases (appearance of new lesions) were recorded (among them seven cases (19.4%) involved also local and/or regional progression), three cases were local metastases, while from the remaining six cases, three were loco-regional only, two were local and one was regional PD.

Metastases were detected in only one site for 21 patients (70.0% of the 30 patients with distant/local metastases), while in two and three sites in 8 (26.7%) and 1 (3.3%) patients, respectively. The lungs were the most frequent metastatic site (25.0%), followed by the brain (17.5%), the lymph nodes (15.0%) and the liver (12.5%) *(Tables S2-S3).*

Safety

Adverse events

The safety cohort consisted of the 77 patients who received at least one dose of treatment, with 76 (98.7%) of them experiencing at least one adverse event (AE). A detailed display of the AEs by grade is provided in Table S4.

Of the total number of 780 AEs, 91 (11.6%) were severe, 20 (2.6%) life-threatening and 10 (1.3%) fatal (Table 2). Seven of the 10 fatal events, are considered at least possibly related to nivolumab, with pneumonitis definitely attributed to nivolumab and possibly related to RT, while oesophageal fistula is definitely related to RT.

In total, 361 AEs were related to at least one treatment, with 168 (21.5%) related to RT, and 249 (31.9%) to nivolumab (Table 2). For 84.5% of these (radiotherapy- or nivolumab-related) events, no action was taken, while for 31 (8.6%), dose was delayed. Only in eight (2.2%) cases the dose was temporarily discontinued and in 16 (4.4%) permanently (one of grade 1, nine of grade 2, five of grade 3, one of grade 5). For 1.6% of cases, no information on the action taken was available.

Serious adverse events

Almost half of the patients in the safety cohort experienced from one to four serious AEs (SAEs) (48.1%). Of the total 61 recorded SAEs, 15 (24.6%) were of grade 2, 29 (47.5%) of grade 3, and eight each for grade 4 (life-threatening) and grade 5 (fatal). Most of them were resolved (75.4%). Only four (6.6%) were attributed to nivolumab.

In total, nine (11.7%) patients experienced a pneumonitis event of grade≥3 (eight of grade 3 and one of grade 5), six of which occurred within 6 months post RT. Seven were resolved completely, one was resolved with sequelae, while one more although initially resolved, re-occurred leading to the patient's death. The median time to event's resolution was 11 days (range: 6-53). All pneumonitis cases were attributed to nivolumab (three with possible, four with probable and two with definite relation) while, four cases were also attributed to RT with a probable relation.

DISCUSSION

Radical, curative-intent, treatment of stage III NSCLC, while extensively studied has remained a medical challenge. While concurrent chemo-radiotherapy has been the standard of care for inoperable disease for a long time, the results of the recent PACIFIC study has defined a new standard by combining CCRT with consolidation durvalumab for 12 months. Despite these clinically meaningful advances, the majority of patients will eventually still die from lung cancer.[6,13] As there is preclinical evidence that the administration of a PD(L)-1 antagonist immediately after or preferably during radiotherapy may be the most efficient[7] way to combine treatment, the NICOLAS trial investigated the concurrent administration of nivolumab with CCRT followed by 12 months of nivolumab. In this trial, we report for the CCRT cohort, a 1-year PFS of 53.7%, a median PFS 12.7 months, a 1-year OS 75.7%, 2-year OS 63.7% and a median OS 38.8 months.

These results could also be viewed in relation to other recent studies such as RTOG 0617,[2] PROCLAIM[5] and PACIFIC[6] (Tables S5, S6). The 1-year PFS was 48% in the 60 Gy arm of RTOG 0617, 48% in the cisplatin-pemetrexed arm of PROCLAIM and 55.9% in the durvalumab arm of PACIFIC. The 1-year OS and median OS for RTOG 0617, PROCLAIM and PACIFIC were 78%, 76%, 83.1% and 28.7 months, 26.8 months, not reached, respectively (at median follow-up times 32.4, 22.2 and 33.3 months accordingly). However, major differences between these studies should be emphasized, using significantly distinct upfront selection criteria. In PACIFIC, patients were randomized after having received CCRT, which is 2-3 months later than in the other studies RTOG, PROCLAIM and NICOLAS, all of which included patients before CCRT. In PACIFIC, only the fittest patients without disease progression after completion of CCRT were enrolled, whereas in NICOLAS, similarly to RTOG 0617 and PROCLAIM, patients had to be in a good general condition at time of enrolment, *before* starting CCRT. In PROCLAIM, only non-squamous histologies (mainly adenocarcinoma) were eligible in view of the use of pemetrexed. In the same study, patients with pleural effusion required a puncture. In case of documented exudate, even in the absence of malignant cells, patients were not eligible for the trial. In RTOG 0617, patients with involvement of supraclavicular lymph nodes were not eligible for the study. In this study, also pleural exudates were excluded, regardless of the cytology. Additionally, patients' demographics also appear to be different between these studies. In NICOLAS, stage IIIB patients, generally characterized with a poorer outcome, were representing 63% of the ITT population, a substantially higher proportion than in PACIFIC (45%), RTOG 0617 (34%) and PROCLAIM (52%). As the inclusion criteria of the present NICOLAS trial were less stringent than in the two other studies, with a NSCLC population characterized with a possibly worse outcome, **an inter-trial comparison is not possible**. Nevertheless, the 1-year PFS of 53.7% in NICOLAS compared to 48%

in RTOG 0617 and 38% in PROCLAIM as well as the median OS of 38.8 months compared to 28.7 and 26.8 months respectively, support continuous investigations of concurrent immunotherapy with CCRT.

As previously published, it is reassuring that the toxicity of nivolumab given together with CCRT was within the predefined limits.[11] Of note, 89% of treatment discontinuations happened during the consolidation phase, with 44% of them being attributed to treatment toxicity. While we could not reject that the 1-year PFS rate is 45% or lower, the safety, PFS and OS outcomes support continued investigation of concurrent nivolumab with CCRT. Ultimately, the impact of using immune checkpoint inhibition concomitantly to chemo-radiotherapy will be determined in larger randomized trials using durvalumab (NCT04092283, NCT03519971) or nivolumab (NCT04026412).

In conclusion, at the present time, the use of checkpoint inhibitors given concurrently with CCRT remains experimental, but this strategy is promising enough to warrant further investigation.

Acknowledgment

We thank all patients who participated in the trial and their families, the NICOLAS investigators at the 10 clinical sites and their teams, the ETOP Independent Data Monitoring Committee (IDMC) and Bristol-Myers Squibb for supporting the trial.

The NICOLAS trial was sponsored and coordinated by ETOP and financed by a grant from Bristol-Myers Squibb.

NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

REFERENCES

1. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28**(suppl_4): iv1-iv21.
2. Bradley JD, Hu C, Komaki RR, et al. Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol* 2020; **38**(7): 706-14.
3. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE). *J Clin Oncol* 2015; **33**(35): 4194-201.
4. De Ruysscher D, van Baardwijk A, Wanders R, et al. Individualized accelerated isotoxic concurrent chemo-radiotherapy for stage III non-small cell lung cancer: 5-Year results of a prospective study. *Radiother Oncol* 2019; **135**: 141-6.
5. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol* 2016; **34**(9): 953-62.
6. Gray JE, Villegas A, Daniel D, et al. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2020; **15**(2): 288-93.
7. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* 2014; **74**(19): 5458-68.
8. Chen D, Menon H, Verma V, et al. Response and outcomes after anti-CTLA4 versus anti-PD1 combined with stereotactic body radiation therapy for metastatic non-small cell lung cancer: retrospective analysis of two single-institution prospective trials. *J Immunother Cancer* 2020; **8**(1).
9. Pitroda SP, Chmura SJ, Weichselbaum RR. Integration of radiotherapy and immunotherapy for treatment of oligometastases. *Lancet Oncol* 2019; **20**(8): e434-e42.
10. Planchard D, Popat S, Kerr K, et al. Correction to: "Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Ann Oncol* 2019; **30**(5): 863-70.
11. Peters S, Felip E, Dafni U, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer-The ETOP NICOLAS trial. *Lung Cancer* 2019; **133**: 83-7.
12. De Ruysscher D, Faivre-Finn C, Nestle U, et al. European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. *J Clin Oncol* 2010; **28**(36): 5301-10.
13. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med* 2018; **379**(24): 2342-50.

NICOLAS: Nivolumab consolidation with standard first-line chemotherapy and radiotherapy in locally advanced NSCLC

TABLES & FIGURES

List of Tables

List of Figures

* The *primary efficacy analysis cohort* consists of the first 74 evaluable patients under concurrent CRT who had either reached 1-y tumour assessment without a PFS event or had earlier experienced a PFS event.

Figure 2: Progression-free survival. A) Progression-free survival (full CCRT cohort; N=79) *(CI band is indicated with dashed lines).* B) One-year progression-free survival rate by patient and treatment characteristics (Full CCRT cohort; N=79). *All p-values from separate Cox models are not significant at α=5%. (Not shown: Never smokers n=3, Missing observations: histology n=4, stage n=1, ECOG PS n=1, chemotherapy regimen n=2)*

Figure 3: Overall survival by histology and stage

A) Overall survival by histology. B) Overall survival by stage

(Full CCRT cohort; N=79) *Note: Missing: histology n=4; stage n=1*

Figure 4: Best % change from baseline for target lesion size (Sum of tumour diameters for targeted lesions) (Among patients with available information in the full CCRT cohort; N=79)

** indicates non-evaluable patients, § indicates patients with missing information on tumour diameters*

Table 1: Patient and treatment characteristics (full CCRT cohort; N=79)

Characteristic	All patients
Before treatment start (N=79)	
Age (years)	
n (%)	79 (100.0)
Mean (95% CI)	62.3 (60.3, 64.3)
Median (Min-Max)	62 (41 - 78)
Gender - n (%)	
Male	53 (67.1)
Female	26 (32.9)
Histology - n (%)	
Non-squamous	47 (59.5)
Squamous	28 (35.4)
Missing	4 (5.1)
Stage - n (%)	
IIIA	28 (35.4)
IIIB	50 (63.3)
Missing	1 (1.3)
Smoking history - n (%)	
Current (patient still smokes)	22 (27.8)
Former (≥100 cigarettes in the past during the whole life)	54 (68.4)
Never (0-99 cigarettes during the whole life)	3 (3.8)
ECOG Performance status at enrollment - n (%)	
0	37 (46.8)
1	41 (51.9)
Unknown/Missing	1 (1.3)
After treatment start (N=77)	
Chemotherapy regimen - n (%)	
Cisplatin	
Etoposide	24 (31.2)
Pemetrexed	20 (26.0)
Vinorelbine	21 (27.3)
Carboplatin (Etoposide/Pemetrexed/Vinorelbine)	12 (15.6)
ECOG Performance status after CRT phase - n (%)	
0	26 (33.8)
1	42 (54.6)
2	3 (3.9)
3	1 (1.3)
4	1 (1.3)
Unknown/Missing	4 (5.2)

Table 2: Treatment related adverse events (safety cohort; N=77)

	Radiotherapy	**Nivolumab**
	n (%)	
Safety cohort	77	76
Any AE *(SAE)*	780 *(61)*	
Treatment related AEs *(SAEs)*	168 *(14)*	249 *(26)*
Treatment related AEs *(SAEs)* Grade 3-5	32 *(9)*	44 *(18)*
Treatment related AEs *(SAEs)* leading to death	2 *(1)*	7 *(6)*
Treatment related AEs *(SAEs)* leading to treatment permanent discontinuation	6 *(-)*	16 *(-)*